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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,945	THOMSEN ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-75,77,78 and 81-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-72, 75, 77-78 and 81-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SSD

DETAILED ACTION

1. Upon due reconsideration, the Finality of the Office Action mailed on June 1, 2005 has been withdrawn.

2. Applicant's response to the Office Action mailed June 1, 2005 on August 30, 2005, is acknowledged.

3. Claims 1-68, 73-74, 76 and 79-80 have been canceled. Claims 69 and 99 have been amended. Claims 69-75, 77-78 and 81-106 are pending. Claims 69-72, 75, 77-78 and 81-106 are under examination.
on applicant's request for withdrawal on page 8 of the amendment filed on August 30, 2005.

Withdrawn-Claim Rejections - 35 USC ∋ 112

4. Previous rejections to claims 83-84 and 98-99 under 35 U.S.C. 112, second for the recitation of "interaction" is withdrawn based on applicant's arguments presented on page 16 of the amendment.

Withdrawn-Specification Objection

5. Previous objection to the specification regarding trademarks is withdrawn by virtue of the amendment.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 69-72, 75, 77 and 88-91 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite added material, which is not supported by the original disclosure. Independent claim 69 recite "wherein the Smurf activity detected is the activity of a Smurf comprising greater than 80% identity with the amino acid sequence depicted in SEQ ID NO:2" and there is no support for this in the instant specification. On page 21 of the specification it is disclosed that "...two amino acid sequences are "substantially homologous" or substantially similar" when greater than 70% of the amino acids are identical, or greater than about 90% are similar (functionally similar)...". There is no disclosed Smurf having the activity of a Smurf with greater than 80% identity to SEQ ID NO:2. It is suggested that applicant delete the above phrase in the claim. Therefore, the specification lacks adequate written description.

Response to Applicant's Arguments:

7. The response on page 12 state that the specification defines the term "about" to mean "within 20%, preferably within 10% and more preferably within 5% of a given range" (page 16 of the specification). Applicant concludes that "about 90%" means, *inter alia*, 90% $\pm$ 10% (i.e. 80%). From this reasoning applicant state that "80% identity" is expressly disclosed in the specification. This argument is not persuasive. Claim 69 (and the dependent claims hereto) recite "comprising greater than 80% identity with the amino acid sequence depicted in SEQ ID NO:2", the instant specification does not provide any support for this language. The specification on page 21 discloses that, "two amino acid sequences are "substantially homologous" or "substantially similar when greater than 70% of the amino acid sequences are identical, or greater than about 90% are similar...", however, this statement does not lead to "80% identity to SEQ ID NO:2", nor does applicant's statement regarding the definition of "about". The definition of "about" does not identify a sequence that is 80% identical to SEQ ID NO:2. Note that claim 75 was inadvertently left out of the above rejection, as the claim depends from claim 69 and does not rectify the deficiency of claim 69, the claim properly belongs in this rejection. Applicant is reminded that the rejection under 35 U.S.C. 102 has been withdrawn in view of the amendments to claim 69, however, the rejection will be reinstated once the new matter is removed.

8. Claims 69-72, 75, 77 and 81-91 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method of screening for a modulator of Smurf activity. Claim 69 for example, has been amended to recite "the activity of Smurf comprising a WW domain and or a HECT domain and comprising greater than 80% identity with the amino acid sequence depicted in SEQ ID NO:2. Note that the recitation of the language "WW domain and or a HECT domain" provides some additional structural information, however, does not provide any functional limitation, as possession of a domain is not *per se* a function. In addition, claims 69 and 77 for example, recite 80% and 90% sequence identity, thus the claimed invention is directed to a large variable genus of proteins, however, the instant specification does not provide adequate description of the genus of polypeptides encompassed in the claims. There is no indicia as to conserved regions of for example SEQ ID NOS: 2 and 4 or where in the sequences the modifications will occur. The instant specification does not adequately describe variants of the claimed sequences by structure or any characteristics to indicate possession of the claimed variants. Further, the claims do not recite any functional limitation to indicate that once modified the protein will retain the specific Smurf activity (see for example claims 69, 75, 77 and 90-91). It is noted that claims such as 70-71 and 88-89, recite a function (i.e. ubiquitination), however, the claims are directed to a large genus of polypeptides for which this function might not be retained and for which all the structural requirements are not met. Therefore, the skilled artisan cannot envision the detailed chemical structure of the polypeptides, thus, claims reciting % identity of the claimed sequences lacks adequate written description.

The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire

genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claimed genus of polypeptides could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed polypeptides encompasses widely variant species. As such, neither the description of the structure and function of SEQ ID NOS: 2 or 4, for example "80% identity to SEQ ID NO:2 ", is not sufficient to be representative of the attributes and features of the entire genus. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity

or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Response to Applicant's Arguments:

9. Note that the rejection of record under 35 U.S.C. 112, first, written description has been restructured based on amendments to the claims and because some claims were inadvertently left out of the rejection. The response on page 10 state that the written description guidelines do not require a description of the complete structure of every species within a chemical genus. Applicant points to *Utter v. Hiraga* and *University of California v. Eli Lilly and Co*. This argument is not persuasive as the written description guidelines requires that a representative number of species of the claimed genus is provided to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus.

It is further stated on page 11, that it is unclear why 80% is inadequate to constitute a substantial portion of the genus. The instant specification does not provide any description of where in the sequence variation will occur or what composition of amino acids will remain in the structure or whether the functions attributed to SEQ ID NO:2 is retained once modified or what conserved regions exist in the structure or whether 20% variability can be tolerated by the instant

sequence. In addition, Applicant is directed to the written description guidelines, which provides examples that specifically address 95% sequence identity coupled with functional language. Moreover, the recitation of WW domain and/or HECT domain does not rectify the deficiency in the claims as that language provides additional structural information, however, does not address the functional limitation issue or provide sufficient structure to describe 20% variability in SEQ ID NO:2.

Applicant on page 11 of the response states that "similarly, claims 7-72 and 77 which depend either directly or indirectly on claim 69 comply with the written description guidelines. However, this statement is not accurate. Note that claims 7-68 have been cancelled in the application and the dependent claims are also included in the rejection because they do not rectify the deficiency of the claims. Therefore, the rejection remains.

10. Claims 92-106 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of screening for a modulator of Smurf activity and the claims do not specify what Smurf protein is being monitored, for example, provide a reference structure. The instant specification on page 24 outlines wild type Smurf1 or Smurf2 (vertebrates) and the art recognizes Dsmurf (Drosophila), thus without a reference point a skilled artisan would not be able to practice the claimed method as claimed. The instant application recognizes that Smurf1 and Smurf2 are structurally and functionally different (see page 13 of the

specification). Thus, the claims lack adequate written description and does not demonstrate possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997)*. Therefore, a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. *See MPEP 2163.*

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of

isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Response to Arguments

11. On page 13 of the response applicant states that claims 70-72 would indicated as allowable if rewritten in independent form, said claims are not 97-99. Note however, that claims 70-72 depended from claim 69 and encompassed those limitations. Claims 97-99 are devoid of a structure, which claims 70-72 had. Claims 70-72 were not written with all the pertinent information from independent claim 69. Thus, applicant's arguments are not persuasive. The applicant state that claims 92, 93, 97 and 98 recite methods of screening for a modulator of Smurf activity and not necessarily Smurf proteins *per se.* This line of reasoning is not persuasive and the protein and the activity go hand in hand. Applicant also lists four distinct activities reported for the Smurf protein, however, the issue in the rejection is whether, the claimed method is adequately described. Claim 92 for example does not set forth which Smurf's activity is being monitored as the art recognizes Smurf1, Smurf2 and Dsmurf as being distinct. Additionally, no distinguishing feature of the Smurf that is being monitored is provided such as structure. Thus, the rejection remains.

12. Claims 78-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of screening for a modulator of Smurf activity and the claims do not specify what Smurf activity is being monitored, for example, ubiquitination of a Smad polypeptide, ubiquitination of a TGFbeta receptor and interaction of a Smurf WW domain with a PPXY domain of Smad polypeptide. The instant specification on page 24 outlines wild type Smurf1 or Smurf2 (vertebrates) and the art recognizes Dsmurf (Drosophila), which are said to have different functions, thus without a reference point a skilled artisan would not be able to practice the claimed method as claimed. The instant application recognizes that Smurf1 and Smurf2 are structurally and functionally different (see page 13 of the specification). Thus, the claims lack adequate written description and does not demonstrate possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997)*. Therefore, the claimed invention should be described by a functional characteristic, or any known or disclosed correlation between that function and the structure of the sequence.

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

13. Claims 69-72, 75, 77 and 88-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the proteins set forth in SEQ ID NOS: 2/4 and the disclosure in Beach et al. (WO 97/12962, April 10, 1997), does not reasonably provide enablement for any polypeptide fragment of SEQ ID NOS: 2/4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of polypeptide fragments. The instant specification indicates that "Smurf proteins of the invention may contain at least about 5 and preferably at least about 10 contiguous amino acids from the sequences set forth in SEQ ID NOS: 2/4" (see page 4). Page 21 of the specification provides a definition of what is considered to be "substantially homologous/similar" and page 24 of the instant specification discloses that

derivatives or analogs are encompassed that are functionally active, i.e. capable of exhibiting one or more functional activities associated with a full-length wild type Smurf. However, the instant specification does not demonstrate any fragments of the claimed sequence having a Smurf activity. It is noted that the prior art discloses ubiquitin ligases (E3) with a sequence that is 77% and 99% identical to the claimed sequences (SEQ ID NO:2 and 4, respectively), however, the disclosed reference does not enable a sequence that is 79%, 80%, 85% to for example SEQ ID NO:2. Additionally, there is no demonstration of such a sequence having the desired activity. The instant protein could be non-functional or have a different function, thus, a skilled artisan would not know what activity to monitor in the claimed method absent guidance/direction. A large quantity of experimentation would be necessary to generate the infinite number of fragments recited in the claims and possibly screen same for activity and with the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance

has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page

2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention (see page 21 of the specification and claim 3, for example).

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of fragments. The claims broadly read on any fragment thereof for the given sequences (SEQ ID NO: 2/4). The issue in this case is the breath of the

claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Response to Arguments

14. The applicant on pages 14+, state that the claimed invention is enabled based on the disclosure and points to pages 23-24, 27-39 and 24-27 for example, providing information of how to clone Smurf family genes, express Smurf family proteins and obtain derivatives. It is also stated that applicant has fully enabled SEQ ID NOS: 2 and 4 and fragments thereof by providing the complete amino acid sequence of SEQ ID NO:2 and 4. However, the skilled artisan cannot envision the detailed chemical structure of the claimed Smurf protein having a 20% variability absent guidance as to where in the sequence the changes are made and what changes are made. The claims broadly read on any fragment of SEQ ID NO:2. The claims do not identify a region that is conserved or specific point mutations that can be tolerated or the amino acids to be substituted, added or deleted. There is no indication of whether or not the modified structure will retain the four functions associated with SEQ ID NO:2, or have a different activity or result in a non-functional protein. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. The art is very clear on the fact that modifications to a protein's structure can affect the protein's structure function relationship. For example, Guo et al. (PNAS, vol. 101, no.25, pages 9205-9210, 2004) disclose that a third of single amino acid changes would completely inactivate the average protein and the more substitutions made the more probability that the protein will be inactivated. Thus, this gives the sense of what one of skill in the art can expect when a claim embraces fragments with up to 10, 20, 30, 40 or more amino acid changes and how many mutants one of

skill in the art can test in such an endeavor. Note that the claim puts no limit on the size of the fragment.

Applicant state that the specification indicates that the Smurf proteins may contain at least about 5 or 10 contiguous amino acids. However, this language is not recited in the claims and the limitations of the specification cannot be read into the claims. Furthermore, the claims are very broad and encompass fragments that are not contiguous. In addition, the specification does not demonstrate said fragments as having the activity claimed for SEQ ID NO:2. Applicant also state that it was routine at the time of filing the instant application in the art to routinely screen for a large amount of mutants using for example high throughout screening assays. This argument is not persuasive as it is in no way predictable what changes can be tolerated in a particular protein sequence. Further, it is not routine in the art to test an infinite number of mutants and determine if they have activity. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Thus, for all these reasons and the reasons of record the rejection remains.

Conclusion

15. No claims are presently allowable. This rejection was not made final although the rejections remain because claims were added to the rejections and based on the restructuring of the rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner

9/22/05

HOPE ROBINSON
PATENT EXAMINER